

Poster

02a: CIRRHOSIS AND COMPLICATIONS - a) PATHOPHYSIOLOGY

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REDUCTION IN AMMONIA WITH L-ORNITHINE, PHENYLACETATE (OP) BUT NOT ANTI-TNF PREVENTS LPS INDUCED BRAIN EDEMA IN BILE-DUCT LIGATED CIRRHOTIC RATS

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Background: Inflammation is thought to be synergistic with ammonia in the pathogenesis of hepatic encephalopathy (HE) but it is unknown whether targeting inflammation and ammonia may be synergistic in reducing brain edema.

Aim: To determine whether administration of L-ornithine phenylacetate (OP), a novel therapy that reduces ammonia levels, when combined with Infliximab (anti-TNF antibody) synergistically prevent LPS induced cerebral edema in bile-duct ligated (BDL) cirrhotic rats.

Method: (n = 28) Sprague-Dawley rats were studied 4-weeks after BDL or Sham-operation. Infliximab (10 mg/kg) treated rats received the drug IP 24 hrs prior to the study; OP (0.6 gm/kg) treated rats received the drug IP 3-hours before termination. All LPS (1 mg/kg) was administered in the LPS groups 3 hours prior to termination. Study groups were (1) Sham, (2) BDL + saline, (3) BDL + LPS, (4) BDL + LPS + OP, (5) BDL + LPS + Infliximab and (6) BDL + LPS + OP + Infliximab. Arterial ammonia, plasma biochemistry, plasma and brain cytokine responses and brain water were analysed (pro-inflammatory TNF- α , IL-6 and γ -IFN and anti-inflammatory IL-4 and IL-10).

Results: Compared with Sham controls, bile duct ligation was associated with significantly higher arterial ammonia (p < 0.05), and marked plasma & brain proinflammatory response (p < 0.01 respectively), though only a minimal trend to increased brain water (ns). Administration of LPS to BDL rats significantly worsened coma stage, brain water and proinflammatory response. Compared to BDL controls, lone OP significantly reduced arterial ammonia and brain water (p < 0.05, respectively). Infliximab lead to a trend to decreased brain water (ns) and no effect on ammonia, though only Infliximab lead to reduced pro-inflammatory cytokine responses (P < 0.05). Co-administration of OP and Infliximab, lead to a marked (though ns) improvement in coma score and brain water; without a synergistic effect on arterial ammonia or pro-inflammatory response compared to lone treatment.

Conclusion: The results of this study show that a reduction in ammonia with OP prevents the deleterious effect of LPS on brain edema indicating that the catastrophic consequences of LPS in BDL animals is related to hyperammonemia, which remains the central target of therapy of HE.